CASWELL FILE 12

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

**MEMORANDUM**

SUBJECT: California Department of Food and Agriculture - EPA Toxicology review for Methidathion. (Tox. Chem. #378B)

FROM: Marion P. Copley , D.V.M., Toxicologist
Section 2, Toxicology Branch 1 (IRS)
HED (TS-769C)
Judith W. Hauswirth for MPC.

THRU: Judith W. Hauswirth, Branch Chief
Toxicology Branch 1 (IRS)
HED (TS-769C)
Judith W. Hauswirth 1/23/89

TO: William Burnam, Acting Division Director
Health Effects Division (TS-769C)

The following responses are provided for each specific deficiency identified by the Medical Toxicology Branch of the California Department of Food and Agriculture regarding methidathion:

**STUDY TYPE:** Chronic dog, (study #not given, Safety evaluation by two-year feeding studies in rats and dogs, Woodard Research Corp., 1/6/67).

Deficiency #1: insufficient histopathology

EPA Response: In 1972, the Agency requested and received additional histopathology slides for the mid and low dose tissues not previously examined and all liver slides. Following reevaluation of these slides, the Agency pathologist (memo dated 8/13/73 from E. Long to C. Williams) determined that adequate information was available to evaluate the microscopic alterations due to methidathion.

Deficiency #2: too few animals, missing electrolyte balance data, no food consumption data.

EPA Response: The above deficiencies will be addressed together with the statement from the DER update, As noted in the Toxicology Chapter of the Final Registration Standard and Tolerance Reassessment (3/11/88)

"There are numerous deficiencies as discussed in the original DERs ... This study however, was completed in 1967 and followed the standard procedures for that time. Most of the suggested analyses (clinical chemistry, histopathology, hematology, body and organ weight, urinalysis and electrocardiograms were completed. Although food consumption was not monitored, the dogs were each given a set [known] amount of food.

"...This is a 2 year study rather than the 1 year currently required .... This study appeared to be well conducted considering that it was completed in 1967.. There are good NOELs and LELs for systemic and cholinesterase effects."

It is unlikely that additional data would alter the conclusions of this study.

**CONCLUSION:** Non-concurrence with California (no data gap).

**CORE-GRADE:** Remains unchanged - core-minimum.

**STUDY TYPE:** DNA Damage, (study #801489, Sister chromatid exchange - study in somatic cells, bone marrow, GS 13005, Chinese hamster, Ciba-Geigy Ltd, Switzerland, 11/4/80).

Deficiency #1: Inadequate number of animals/cells scored (in view of elevation in SCE at mid dose)

EPA Response: Although there was a statistical increase in SCEs at the mid dose, it was not marked and in view of the lack of a dose response, and other negative studies for DNA damage (although supplementary) it is unlikely that this increase is biologically significant. The Agency agrees that more animals should have been evaluated. However, additional studies with more animals would not be expected to alter the conclusions of this study.

**CONCLUSION:** Non-concurrence with California (no data gap).

**CORE-GRADE:** Remains unchanged - core-acceptable.

**STUDY TYPE:** Neurotox, (study #Siss 5927, Acute Oral toxicity and neurotoxicity study of technical GS-13005 in the domestic fowl, Ciba-Geigy Corp, 9/25/78).

Deficiency #1: No forced motor activity or body weight data.

EPA Response: Although these endpoints would be of interest they are not required by the guidelines. An additional study would not be expected to alter the conclusions of this study.

Deficiency #2: No histopathology on thoracic spinal cord or medulla oblongata.

EPA Response: There was histopathology of the spinal cord (lumbar) and peripheral nerve. It is unlikely that additional histopathology would alter the conclusions since there was no clinical evidence of delayed neuropathy following two sequential 21 day dosing periods (with atropine pretreatment.

It is unlikely that additional data would alter the conclusions of this study. In addition the O,O-dimethyl organophosphate derivative is not likely to be a delayed neurotoxic.

**CONCLUSION:** Non-concurrence with California (no data gap).

**CORE-GRADE:** Remains unchanged - core-guideline.

CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH
SUMMARY OF TOXICOLOGY DATA

METHIDATHION (SUPRACIDE)

SB 950-094, Tolerance # 298

November 21, 1986
Revised November 16, 1987
Revised April 29, 1988
Revised July 11, 1988
Revised October 7, 1988

I. DATA GAP STATUS

COMBINATION (CHRONIC & ONCO) RAT: No data gap; No adverse effect.

COMBINATION (CHRONIC & ONCO) MOUSE: No data gap; Possible adverse effects in both areas.

CHRONIC DOG: Data gap; Inadequate study; Possible adverse effect indicated.

REPRO RAT: No data gap; No adverse effect.

TERATO RAT: No data gap; No adverse effect.

TERATO RABBIT: No data gap; No adverse effect.

GENE MUTATION: No data gap; No adverse effect.

CHROMOSOME MUTATION: No data gap; Possible adverse effect.

DNA DAMAGE: Data gap; Inadequate studies; No adverse effect indicated.

NEUROTOX: Data gap; Inadequate studies; No adverse effect indicated.

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**Note, Toxicology one-liners are attached**

** indicates acceptable study
**Bold face** indicates possible adverse effect
File name: T881007
Summary of Toxicology Data updated by B. K. Davis 11/16/87; updated by M. Silva 4/29/88 and 7/11/88; updated 10/7/88 by J. Gee.

Jan. PCC CTR.

J. Parker 10-7-88
J. Gee 10/7/88

COMBINATION RAT:

** 090 (5 volumes) 053935 "Methidathion - 2-Year Oral Oncogenicity and Toxicity Study in Albino Rats," (CIBA-GEIGY 5/23/86) Methidathion (97.3%) at 0, 4, 40 and 100 ppm in the diet to 80 Sprague-Dawley rats/sex/group in a two year study; 20/sex/group for clinical studies; interim sacrifices of 10/sex/group at 52 weeks and 5/sex/group at 93 weeks; oncogenicity NOEL > 100 ppm; chronic toxicity NOEL = 4 ppm (skin lesions/sores with ulceration and inflammation, transient neurological effects, altered blood parameters, altered biochemical parameters, reduced liver weights, alveolar foamy macrophages) No adverse effect; Acceptable (Davis 10/28/87).

COMBINATION MOUSE:

** **079 through 087 45719-45727** "Two Year Dietary Oncogenicity Study in Mice," International Research and Development Corp., 3/7/86; Methidathion Technical (purity not stated) at 0, 3, 10, 50, and 100 ppm by feeding to 50/sex/dose for 23 months in the oncogenicity phase and to 120/sex/dose with 4 interim sacrifices before the termination at 18 months of the chronic toxicity phase. This includes a group given a one month recovery period on control feed and then sacrificed at 13 months. Possible chronic toxicity adverse effect: increased mortality, discolored urine in males at high doses, some elevated blood enzymes, altered cholinesterase levels, multiple liver and gallbladder changes, some spleen changes. NOEL = 10 ppm = 1.2 to 2.0 mg/kg/day. Possible oncogenicity adverse effect: increased frequencies of hepatocellular adenomas and carcinomas as well as nonneoplastic hepatic and bilary changes in males at 50 and 100 ppm, increased frequencies of nonneoplastic hepatic changes in females at 100 ppm. Complete Acceptable. (B. Davis, 11/14/86)

CHRONIC RAT:

A possible adverse effect was identified in the following study based on the slight increase in the frequency of degenerative liver changes in high dose animals. Noting that this effect was slight and that the study had numerous deficiencies which made it unacceptable, the present reviewers are more convinced by the lack of chronic toxicity in the acceptable combined rat study (Record 053935). The high dose (100 ppm) in the combined study was somewhat greater than that of the chronic study (64 ppm), yet no degenerative liver changes were found. B. Davis, 1987.

**010 935997** "Safety Evaluation by 2-Year Feeding Studies in Rats and Dogs - GS 13005, 40W - Rat Study," Woodard Research, 1/6/67; Rat chronic toxicity (831). Methidathion (GS 13005 - 40% wettable powder, purity not stated) at 0, 4, 16, 64 ppm in feed to 25/sex/dose for 100 weeks; Possible adverse effect--degenerative liver changes, decreased adrenal-to-body and ovary-to-body weights, increased kidney ratios, decreased body weight gain. NOEL <4 ppm. Incomplete Unacceptable. High mortality (85/200) from pulmonary infections, hematology sampling insufficient, blood biochemistry too limited, missing individual data, incomplete histopathology. (J. Remsen, 7/5/85, Davis 11/10/87)

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CHRONIC DOG:

**010 33538** "Safety Evaluation by 2-Year Feeding Studies in Rats and Dogs - GS 13005, 40W - Dog Study," Woodard Research, 1/6/67; Methidathion (GS 13005 - 40% wettable powder, purity not stated) at 0, 4, 16, 64 ppm in feed 6 days/week for 105 weeks to 3 Beagles/sex/dose. Possible adverse effect--dark liver pigmentation, some pigmentation of hepatic cells, slight kidney cell pigmentation, altered plasma enzyme levels suggestive of altered liver metabolism. NOEL = 4 ppm. Incomplete, Unacceptable. Too few animals, missing electrolyte balance data, insufficient histopathology, no food consumption data. (J. Remsen, 7/5/85).

CHRONIC MONKEY:

014 935999 "Two-Year Safety Evaluation in Rhesus Monkeys," Institute of Experimental Pathology & Toxicology, 4/71; Methidathion (GS 13005, purity not stated) at 0 mg/kg (7 males and 5 females), 0.25 mg/kg (6/sex), 1.0 mg/kg (7 males and 5 females) by gavage 6 days/week for 23 months to Rhesus monkeys. RBC and plasma cholinesterase somewhat depressed. Chronic toxicity NOEL = 1.0 mg/kg. Insufficient information to assess possible adverse effect. Incomplete Unacceptable. Only two dose levels and high dose too low; missing histopathology, individual data. (J. Remsen, 7/8/85)

ONCO MOUSE:

This mouse oncogenicity study (935007) and the mouse combination study (see Records 45719-45727 above) are consistent in indicating induction of liver adenomas and carcinomas. The data gap is filled by the combination study. Davis, 1987.

**016 936007** "Carcinogenicity Evaluation with Methidathion Technical in Albino Mice," Industrial Biotest Laboratories #8580-09380, 5/2/80; EPA Tracking System Report (7/83) rates the study as Supplemental (portions of the study are valid), Pending (still under review), and Replaced (done or in progress); Validation review by registrant in accordance with EPA criteria included (Reports 2 & 4, Record #936006, Vol. 016); Methidathion (98.8% purity) at 0, 10, 100 ppm in feed to 60/sex/dose over 18 months for males and 19 months for females. Possible adverse effect--liver adenomas and carcinomas, spleen nodules. NOEL = 10 ppm. Incomplete, Unacceptable. High dose insufficient to produce chronic toxicity; no food consumption data; negative control group mistakenly dosed in month 14; apparent degradation of test material in first 8 months; no hematology. (J. Remsen, 7/8/85)

REPRO RAT:

097 55142 "Two-Generation Reproduction Study in Albino Rats with Methidathion Technical." Pilot study for 55143. M. Silva, 2/3/88.

** 298-098 55143 "Two-Generation Reproduction Study in Albino Rats with Methidathion Technical," (American Biogenetics Corporation Study 450-2125, 1/15/87). Methidathion technical, 95%, was given to CR1:CD BR rats in the diet at 0, 5, 25 or 50 ppm for a two generation, 1 litter per generation

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reproduction study (15 males and 30 females/dose group). Parental NOEL ppm (decreased: body weight gain--F0 females & F1 both sexes at 50 ppm, foo consumption--F0 females at 25 & 50 ppm & F1 both sexes at 50 ppm, liver & ovary or testes weights--F0 & F1 both sexes at 50 ppm, mating index--F0 & F1 males at 50 ppm; also poor maternal care and tremors during lactation were observed--F0 & F1 dams at 25 & 50 ppm). Reproductive NOEL = 5 ppm. Lower survival and body weights were observed in progeny of both generations at 25 and 50 ppm. No adverse effect. Acceptable. D. Shimer, 12/8/87. M. Silva, 1/28/88.

**018, 076 33539** "GS 13005, 40W - Three-Generation Reproduction Study in the Rat," Woodward Research, 8/18/66; Methidathion (40% wettable powder) at 0, 4, 32 ppm in feed to 10 males and 20 females over 3 generations. Possible adverse effect--decreased weanling survival in most litters. NOEL = 4 ppm. Incomplete, Unacceptable. Report is summary with one data table. (J. Remsen, 7/8/85).

Summary: The more recent, acceptable study did not indicate reproductive effects in the absence of parental toxicity. Therefore, the possible adverse effect in the summary report was not confirmed. Overall, there is not an adverse effect on reproduction. Gee, 10/7/88.

TERATOLOGY RAT:

094 55138 "Methidathion Technical: A Dose Range finding study in Pregnant Rats (MIN852171)." Pilot study for 55139. M. Silva, 2/3/88.

** 298-095 55139 "Methidathion Techncial - A Teratology (Segment II) Study in Rats (MIN 862164)," (Ciba-Geigy, Research Department, Pharmaceuticals Division, Report no. 86172, 1/15/87). Methidathion technical, 95%, was given to mated Crl:COBS CD (SD) BR rats (25/group) by gavage on days 6-15 of gestation (day 0 = presence of sperm in vaginal washing), at 0 (3% cornstarch with 0.5% Tween 80), 0.25, 1.0 or 2.5 mg/kg/day. Fetuses were delivered by caesarean section on gestional day 20. No adverse effects.Maternal NOEL = 1.0 mg/kg/day, (mortality, reduction in food consumption and body weight gain, lethargy, tremors, lacrimation, salvation, raspy respiration, exophthalmia and vaginal blood). Developmental NOEL $\geq$ 2.5 mg/kg/day. Acceptable. D. Shimer, 12/7/87. M. Silva, 1/25/88.

072 1179 "Reproduction Study on GS13005 Technical: Rat," Ciba-Geigy Limited, Basel, Switzerland 2/9/76; Methidathion (GS 13005 Technical, no purity stated) by gavage to female rats on days 6-15, 0 mg/kg to 24 rats, 1 mg/kg to 28 rats, 2.5 mg/kg to 23 rats, 5.0 mg/kg to 21 rats. Maternal toxicity--decreased food intake and body weight gain, tremors. NOEL = 1 mg/kg. Developmental toxicity--incompletely ossified fifth sternebrae. NOEL = 2.5 mg/kg. Insufficient information to assess possible adverse effects. Incomplete, Unacceptable. No individual data, body weight data, uterine weight data, dam autopsy, fetal sex data, corpora lutea data. (J. Remsen, 7/8/85)

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TERATOLOGY RABBIT:

096 55141 "Rabbit - Segment II- Dose Range- Find Teratology Pilot (P-2) Methidathion (MIN 852223)." Pilot Study for 55140. M. Silva, 2/3/88.

** 096 55140 "Methidathion A Teratology (Segment II) Study in Rabbits (MIN 852202)," (Ciba-Geigy, Research Department, Pharmaceuticals Division, Report No. 86131, 1/13/87). Methidathion technical, 95%, was administered to inseminated New Zealand White Rabbits by gavage on days 7-19 of gestation (day 0 = day of artificial insemination) at 0, (3% cornstarch containing 0.5% Tween 80), 2,6 or 12 mg/kg/day (19/group). Fetuses were delivered by Caesarian section on gestation day 29. No adverse effect. Maternal NOEL = 6 mg/kg/day, (ataxia, tremors and salivation). Developmental NOEL $\geq$ 12 mg/kg/day. Acceptable. D. Shimer, 12/8/87. M. Silva, 1/25/88.

GENE MUTATION:

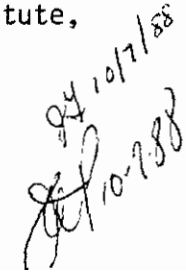
Following are one-liners for gene mutation assays. The 7 Ames Salmonella assays (4 with methidathion and 3 with related compounds) and one E. coli assay include results from 3 different laboratories. The remaining 3 studies are host-mediated assays. Although none of the 11 studies was in itself acceptable, together they present a consistent and compelling picture of no mutagenicity. Therefore the data gap is filled and there is no evidence for an adverse effect. Davis, 1987.

003 936024 "Salmonella/Mammalian-Microsome Mutagenicity Test with GS 13005," Ciba-Geigy Limited, Basel, Switzerland 4/17/80. Methidathion (GS 13005 - purity not stated) at 0, 25, 75, 225, 675, 2025 ug per 0.1 ml $\pm$ activation with triplicate plates of strains TA98, TA100, TA1535, TA1537. Insufficient information to assess mutagenicity. Incomplete, Unacceptable. Positive control with activation done only with TA1535, missing individual plate data, deficient test article characterization. (J. Remsen, 7/3/85)

003 936025 "Salmonella/Mammalian-Microsome Mutagenicity Test with GS 13005," Ciba-Geigy Limited, Basel, Switzerland, 10/29/80. Methidathion (GS 13005 - purity not stated) at 0, 25, 75, 225, 675, 2025 ug per 0.1 ml $\pm$ activation with triplicate plates of strains TA98, TA100, TA1535, TA1537. Insufficient information to assess mutagenicity. Incomplete Unacceptable. Positive control with activation done only with TA1535, missing individual plate data, deficient test article characterization. (J. Remsen, 7/3/85)

003 33537 "In Vitro Microbial Assays for Mutagenicity Testing of DMTP (Methidathion) - Reverse Mutation - Plate Method Using S. typhimurium," Nomura Research Institute, Japan 8/31/79. Methidathion (99.95% purity) at 0, 10, 50, 100, 500, 1000, 5000 ug/plate $\pm$ activation using TA98, TA100, TA1535, TA1537, TA1538. Insufficient information to assess mutagenicity. Incomplete, Unacceptable. No confirmatory assay, positive control results for TA1535 with activation and TA98 without activation both questionable, duplicate rather than triplicate plates/concentration, missing individual plate data. (J. Remsen, 7/3/85)

003 936020 "In Vitro and In Vivo Microbiological Assays of Six Ciba-Geigy Chemicals-Ames Microbial Mutagenesis Assay", Stanford Research Institute,



3/77. Methidathion (purity not stated) at 0, 10, 50, 100, 500, 1000, 5000 ug/plate ± activation using TA98, TA100, TA1535, TA1537, TA1538 with confirmatory assay. No mutagenicity indicated. Incomplete Unacceptable. No statement of number of plates/concentration, no statistics, missing individual plate data, too little test article characterization, some positive controls not done or ineffective. (J. Remsen, 7/5/85)

003 936020 "In Vitro and In Vivo Microbiological Assays of Six Ciba-Geigy Chemicals-Host Mediated Assay", Stanford Research Institute, 3/77. Methidathion (purity not stated) in acute assay with a single dose of 0, 10, 20, 40 mg/kg and subacute assay with 0, 5, 10, 20 mg/kg for 5 days. The number of mice ranged from 6-10 per group. Salmonella strains TA1535 and TA1538 injected ip and recovered from peritoneal cavity after 4 hours. Insufficient information to assess mutagenicity. Incomplete Unacceptable. No evidence for actual exposure of bacteria to test material, missing individual plate data, deficient test article characterization. (J. Remsen, 7/5/85)

003 33536 "In Vitro Microbial Assays for Mutagenicity Testing of DMTP (Methidathion) - Reverse Mutation - Plate Method Using E. coli," Nomura Research Institute, Japan 8/31/79; Methidathion (99.95% purity) at 0, 10, 50, 100, 500, 1000, 5000 ug/plate ± activation using strain WP2 Hcr-. Negative for mutagenicity. Incomplete Unacceptable. No confirmatory assay, duplicate rather than triplicate plates/concentration, missing individual plate data. (J. Remsen, 7/3/85)

003 936026 "Intrasanguine Host-Mediated Assay with S. typhimurium with GS [illegible]-Geigy 10/31/80. Methidathion (purity not stated) administered orally to groups of 6 mice at 0, 5, 10, 20 mg/kg/hour for 3 doses with Salmonella strains TA98, TA100, or TA1537 injected into the tail vein immediately after the third dose. Bacteria recovered from homogenized liver after one hour and assayed for the number of mutants. Insufficient information to assess mutagenicity. Incomplete Unacceptable. No evidence for actual exposure of bacteria to test material, no positive control, lacks TA1535, excessive mortality, missing individual plate data, deficient test article characterization. (J. Remsen, 7/3/85)

003 936022 "Salmonella/Mammalian-Microsome Mutagenicity Test with GS 12956" Ciba-Geigy, Basel, Switzerland 10/27/80. Methidathion metabolite (GS 12956 - purity not stated) at 0, 10, 30, 90, 270, 810 µg per 0.1 ml ± activation with triplicate plates of TA98, TA100, TA1535, TA1537. Insufficient information to assess mutagenicity. Supplementary Study-assay of metabolite. (J. Remsen 7/5/85).

003 936018 "Salmonella/Mammalian-Microsome Mutagenicity Test with GS 28370," Ciba-Geigy ltd., Basel, Switzerland, 10/24/80; Sulfone derivative of methidathion (purity not stated) at 0, 25, 75, 225, 675, 2025 ug per 0.1 ml ± activation with triplicate plates of TA98, TA100, TA1535, TA1537. Insufficient information to assess mutagenicity. Supplementary study-assay of sulfone derivative. (J. Remsen, 7/5/85).

003 936023 "Salmonella/Mammalian-Microsome Mutagenicity Test with GS 28369," Ciba-Geigy, Basel, Switzerland, 12/15/80. Sulfone derivative of methidathion (purity not stated) at 0, 15, 30, 60, 120, 240, 480, 960 ug per 0.1 ml ± activation with duplicate plates of TA98, TA100. Insufficient

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information to assess mutagenicity. Supplementary study-assay of sulfone derivative. (J. Remsen, 7/5/85)

Mammalian cells

003 936017 "Point Mutation Assay with Mouse Lymphoma Cells, Host Mediated Assay with GS 13005," Ciba-Geigy, Basel, Switzerland, 10/21/80. Methidathion (purity not stated) given orally at 0 or 15 mg/kg to 4 mice/dose, 3 days after ip inoculation of mouse L5178Y cells. 3 days after methidathion dosing, L5178Y cells removed from peritoneal cavity and tested for forward mutation. Insufficient information to assess mutagenicity. Incomplete Unacceptable. No evidence for actual exposure of bacteria to test material, no positive control, deficient detail on cell viability or replicates, no GLP, deficient test article characterization. (J. Remsen, 7/5/85)

CHROMOSOME MUTATION:

An overall conclusion cannot be made from the four chromosome mutation studies which have been submitted. The SCE study had a significantly elevated frequency at the intermediate dose but not at the high dose. The two micronucleus assays and the dominant lethal assay were all negative. Furthermore, one of the micronucleus assays was a supplementary study with a methidathion metabolite. The data gap is filled but in the absence of better evidence a possible adverse effect is identified. Davis, 1987 and Gee, 10/7/88.

**003, 103 936027, 067219** "Sister Chromatid Exchange Study - GS 13005 - Chinese Hamster." (Ciba-Geigy, Basle, Switzerland, 11/4/80, supplement dated 5/26/87) Methidathion, Batch op. 25-572, 93.4%; tested at 0 (0.5% aqueous carboxymethylcellulose), 17, 34 or 68 mg/kg by oral gavage given once; BrdU given 2 hours before the test material; 4/sex/group Chinese hamsters; sacrificed after 24 hours; examined slides from 2/sex/group only, 25 cells per animal scored; possible adverse effect with statistically increased ($p < 0.01$) at mid dose. Record # 067219 contains purity, batch number, explanation of using only 2/sex. Unacceptable (inadequate number of animals/cells scored especially in view of the elevation in sister chromatid exchanges at the mid dose. No change in status with submission of supplemental information. Gee, 7/5/85 and 10/6/88.

003, 103 936021, 067218 "Nucleus Anomaly Test in Somatic Interphase Nuclei of Chinese Hamster." (Ciba-Geigy, Basle, Switzerland, 7/2/80, supplement dated 5/26/87) Methidathion, 96.9%, given by oral gavage at 0 (CMC), 17, 34 or 68 mg/kg twice at a 24 hour interval; sacrifice at 24 hours after the second dosing; 6/sex/group with the best slides from 3 animals per sex per group scored; 1000 bone marrow cells per animal; micronucleus test; initially reviewed by J. Remsen, 7/5/85, as unacceptable based on number of animals examined, the single sacrifice time and dose selection not justified. Record # 067218 in 103 describes the criteria used, the selection of doses and slides for scoring. No change in status. No increase in micronuclei formation. Unacceptable (inadequate number of animals scored, no data supporting the sacrifice time.) Gee, 10/5/88.

** 013, 103 936073, 067217 "Dominant Lethal Study in GS 13005 - Mouse." (Ciba-Geigy, Basel, Switzerland, 8/3/76 and 5/26/87) Methidathion,

Batch No. 32289/4239, 98.4%; given by gavage to 20 male NMRI mice per group at 0 (carboxymethylcellulose), 15 or 45 mg/kg; mated over 6 weekly periods at 1 male to 2 females; toxicity included ataxia, diarrhea, somnolence, convulsions and 4/20 deaths at the high dose; no dominant lethal effects reported; initially reviewed as unacceptable (lack of purity, no positive control data) - Remsen, 7/8/85. Record # 067217 contains purity and positive control data with thiotepa in the same strain of mice in the same year. Upgraded to acceptable status. Gee, 10/5/88.

003 936028 "Nucleus Anomaly Test in Somatic Interphase Nuclei - GS 12956 - Chinese Hamster Test for Mutagenic Effects on Bone Marrow Cells" Ciba-Geigy, Basel, Switzerland, 10/30/80. Methidathion metabolite (GS 12956 - purity not stated) at 0, 121, 242, 484 mg/kg/day for 2 days by gavage to 3/sex/dose. Sacrificed 24 hours after second dose and 1000 bone marrow cells/animal evaluated. Micronucleus assay protocol, though scored other nuclear anomalies as well. Insufficient information to assess possible adverse effect. Supplementary Study-assay of metabolite. (J. Remsen 7/5/85)

DNA DAMAGE:

There are five submitted studies in this category as well as the SCE study (see Record 936027 in the Chromosome Mutation category), which can be used in this category. As noted above, the frequency of SCEs was significantly elevated only at the middle dose level. This was identified as a possible adverse effect for the Chromosome Mutation category and will not be considered further here. The five studies which are summarized below were all negative. Although the data gap is not presently filled by these studies, they could be upgraded if more information were supplied. Davis, 1987.

003 936019 "In Vitro Microbial Assays for Mutagenicity Testing of DMTP (Methidathion) - Rec Assay" Nomura Research Institute, Japan, 8/31/79. Methidathion (99.95% purity) at 0, 250, 500, 1250, 2500, 5000, 10000 ug/well without activation using paired Bacillus subtilis strains H17 and M45. Negative for mutagenicity. Incomplete, Unacceptable. No activation included, reference to publication rather than detailed protocol. (J. Remsen, 7/3/85)

089 53774 "The Hepatocyte Primary Culture/DNA Repair Assay on Compound GS-13005-008266 Using Mouse Hepatocytes in Culture." (Naylor Dana Institute 2/10/82) Methidathion = GS-13005-008266 (No purity stated) tested at 14 concentrations from $5 \times 10^{-7}$ to 1%; cytotoxicity at levels $\geq 5 \times 10^{-3}$%; No increase in UDS indicated, Incomplete, Unacceptable (need substance purity and grade, number of cells examined). Davis 10/28/87.

089 53775 "The Hepatocyte Primary Culture/DNA Repair Assay on Compound GS-13005-008266 Using Rat Hepatocytes in Culture." (Naylor Dana Institute 2/10/82) Methidathion = GS-13005-008266 (No purity stated) tested at 10 concentrations from $5 \times 10^{-9}$ to 1%; cytotoxicity at levels $> 5 \times 10^{-2}$%; No increase in UDS indicated, Incomplete, Unacceptable (need substance purity and grade, number of cells examined). Davis 10/28/87.

089 53776 "Autoradiographic DNA-Repair Test on Rat Hepatocytes - GS-13 005 (In Vitro Test for DNA-Damaging Properties)." (CIBA-GEIGY Ltd. No date given) Methidathion = GS-13 005 (no purity stated) tested at 0, 0.128, 0.64, 3.2, or 16 ug/ml; 100 mM DMN as positive control; No adverse effect reported,

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Incomplete, Unacceptable (deficient information on test material, protocol, and results; background not counted; missing page 5. Davis 10/28/87.

089 53777 "Autoradiographic DNA Repair Test on Human Fibroblasts - GS 13 005 (In vitro test for DNA-damaging properties)." (Ciba-Geigy Ltd. 10/18/82) Methidathion = GS 13 005 (no purity stated) tested at 1.024, 5.12, 25.6, and 128 ug/ml; 5 uM 4-nitroquinoline-N-oxide as positive control; No adverse effect reported, Incomplete, Unacceptable, Not Upgradeable (No activation system used, background grain counts not done, missing protocol information, missing test material information, missing results) Davis 10/28/87.

NEUROTOX:

The three submitted studies do not fill the data gap. 935981 is deficient in several aspects as noted in the one-liner, but might be used in support of another study. 16554 used only 4 hens and like the feeding study (14846) is not an acute study.

012 935981 "Neurotoxicity Study in Domestic Fowls, 42 Days - Using GS 13005," Ciba-Geigy, no date. Technical methidathion (GS 13005 -no purity stated) by gavage after pretreatment with atropine sulfate, observed for 21 days, repeated dose and 21 day observation; 0 mg/kg to 10 hens, 43.75 mg/kg to 15 hens, 87.5 mg/kg to 15 hens, 175 mg/kg to 30 hens, 350 mg/kg to 30 hens. Insufficient information to assess possible adverse effect. Incomplete Unacceptable. No forced motor activity, no body weight data; no histopathology on thoracic spinal cord or medulla oblongata. (J. Remsen, 7/5/85)

076 16554 "Toxicology of GS 13005 - Neurotoxicity," Conducting Laboratory not identified, no date. Methidathion (GS 13005 - no purity stated) given by 4 weekly subcutaneous injections to 4 hens at 50 mg/kg. Report is a very a brief summary with insufficient information for assessment. Incomplete Unacceptable. No protocol, data summaries, individual data, negative or positive control groups. (J. Remsen, 7/8/85)

076 14846 "GS-13005, 40 W - Demyelination Study in the Chicken," Woodard Research, 6/18/65. Methidathion (GS 13005 - 40% wettable powder) fed for 45 days to 10 hens/dose at 16, 52, and 160 ppm. Report is a summary with insufficient information for assessment. Liver discoloration at high dose. Incomplete Unacceptable. No protocol, data summaries, individual data, negative control group. Since feeding study, not appropriate for acute delayed neurotoxicity. (J. Remsen, 7/8/85)

ADDITIONAL STUDIES

DERMAL SUBCHRONIC RABBIT:

092 55136 "10-Day Dermal Dose Range Finding Study in Rabbits with Methidathion Technical." (Hazleton, Vienna, VA, Study No. 483-253, 1-16-87). Pilot Study for 55135 and 55137. M. Silva, 2/3/88.

RF 10/7/88

10-7-88

092 55135 "Methidathion 21-Day Dermal Toxicity Study in Rabbits (MIN 852128)." (Ciba-Geigy, Research Department, Pharmaceuticals Division, report no. 86019, 8-28-86) Methidathion technical, 95%, was administered to New Zealand White rabbits dermally (non-occlusion exposure) for 6 hrs/day for 22 consecutive days at 0 (polyethylene glycol 300), 1, 5 or 20 mg/kg/day, 5/sex/group. NOEL > 20 mg/kg/day. One high dose male exhibited hypoactivity, diarrhea, soft feces and decreased food consumption. High dose males as a group had a minimal (not significant) decrease in body weight. No adverse effects. Supplemental Study. No MTD reached. Shimer, 12-15-87. M. Silva, 2/3/88.

093 55137 "21-Day Dermal Toxicity Study in Rabbits with Methidathion Technical." (Hazleton, Vienna, VA, study no. 483-254, 1-16-87) Methidathion technical, 95%, was administered to New Zealand White rabbits dermally (rubber dam occlusion), 6 hours/day for 21 consecutive days at 0 (polyethylene glycol 400), 1, 10, 40 or 80 mg/kg, 5/sex/group. Deaths include 2 at 1 mg/kg, 2 at 10 mg/kg, 5 at 40 mg/kg and 7 at 80 mg/kg. Clinical symptoms increased with increasing dose. They included anorexia, languid behavior, ataxia, hunched posture, labored respiration, soft feces, low body temperature and tremors. Plasma, RBC and brain cholinesterase was significantly reduced at $\geq$ 10 mg/kg. Adverse effects indicated. In the liver, capsular/subcapsular necrosis and acute inflammation was observed in females at 10, 40 and 80 mg/kg. The gallbladder of females in the 10, 40 and 80 mg/kg and males in the 80 mg/kg groups showed caseous necrosis with hemorrhage and chronic serosal inflammation. Supplemental study. Shimer, 12-15-87. M. Silva, 2/2/88.

DERMAL ACUTE, RABBIT:

091 55134 "Rabbit Acute Dermal Toxicity." (Stillmeadow Inc., Houston, Texas, project no. 4272-86, 8-27-86) Methidathion 50S, 50.9%, was dermally applied (non-occlusion) to 5 male and 5 female New Zealand White Rabbits for a period of 24 hours at 2010 mg/kg. The rabbits were observed for 14 days. No adverse effects. $LD_{50}$ > 2010 mg/kg. (1 death occurred, diarrhea, lacrimation, nasal discharge, activity decrease, absent or decreased urination and defecation; gastrointestinal tract distended with gas). Supplemental Study (analysis of analysis of formulated material is required). Shimer, 12-14-87. M. Silva, 2/3/88.

10/7/88
10-3-88

CASWELL FILE
pc 100301

ATTACHMENT

California Department of Food and Agriculture
Medical Toxicology Response
EPA Memorandum Regarding EPA/CDFA Study Acceptability Status for
SB 950 # 094 Reviews of Methidathion Studies
EPA Memorandum Date: 1/23/89
CDFA Response Date: 12/15/89

We have reviewed the EPA Health Effects Division memorandum of 1/23/89 concerning differences between CDFA and EPA study acceptability status for Methidathion. As a result of CDFA reconsideration for all cases in which disagreement was found, no changes were made. Where appropriate, an item by item discussion of study deficiencies discussed by EPA is presented below. New evaluation worksheets and a new Summary of Toxicology Data are routinely provided whenever changes in acceptability status are made.

**SUMMARY OF STUDY TYPES FOR WHICH DATA GAP STATUS DIFFERS BETWEEN EPA and CDFA: INITIAL STATUS COMPARISON WAS MADE BY EPA IN RESPONSE TO PETRIS LETTER. ONLY CASES IN WHICH CURRENT CDFA STATUS DIFFERS FROM EPA STATUS AT THE TIME OF EPA MEMO PREPARATION ARE LISTED HERE.**

Methidathion

| as of (1/23/89) | CDFA Data Gap 12/15/89 | EPA Data Gap 1/23/89 |
|---|---|---|
| **STUDY TYPE** | | |
| Chronic, dog | gap | no gap |
| Neurotoxicity, hen | gap | no gap |

**STUDY TYPE:** Chronic, dog (010 033538) Safety Evaluation by 2-Year Feeding Studies in Rats and Dogs, Woodard Research Corp., 1/6/67.

CDFA received a rebuttal document from Ciba-Geigy regarding the chronic dog (010 033538) and chronic monkey (014 935999) studies. After re-evaluation, it was decided that the two studies could be considered together as acceptable for filling the data gap upon receipt of the following information:

**DOG STUDY:**

a) Clarification of feeding schedule for dogs. "Five mornings a week each dog received 200 grams of Dietrich and Gambrill baked dog meal, supplemented with 70 grams of a canned beef preparation and mixed with water. Double these quantities were provided on Saturdays." Does that mean that the dogs were not fed on Sundays?

b) Proof that Methidathion in a wettable powder form has the equivalent bioavailability of Methidathion technical grade. Methidathion was used as a 40% wettable powder in the dog study.

c) An analysis of dosing material in the diet for homogeneity, concentration and stability must be provided. If dose preparation records plus analytical data are not available from the original dog study, a retrospective analysis may be acceptable.

M. Silva 12/15/89

Charlie N Adams
1/24/90

d) It is not clear from the protocol whether or not an eye exam was performed. An eye examination (ophthalmological exam) was not mentioned in the methods section however, in the results it was mentioned that "Results of eye examinations were unexceptional. Careful neurological examination of each dog at 104 weeks showed no abnormalities."

**MONKEY STUDY:**

a) Grade of Methidathion used in this study was not specified. The lot# GS13005 was mentioned and it is assumed to be the same as the technical grade mentioned in the chemical analysis report (DPN/Volume/Record#: 298/076/935935), however, this was not indicated in this study.

b) An analysis of dosing material for homogeneity, concentration and stability must be provided. If dose preparation records plus analytical data are not available from the original monkey study, a retrospective analysis may be acceptable.

**Conclusion:** Due to the fact that the requested data have not been received as of 12/15/89, there is no change in status for the chronic dog or the chronic monkey at this time.

**STUDY TYPE:** DNA Damage (study 003, 103 936027, 067219), Sister Chromatid Exchange - Study in Somatic Cells, Bone Marrow, GS 13005, Chinese hamster, Ciba-Geigy, Ltd., Switzerland, 11/4/80.

On 5/26/87, CDFA received additional data for this study. The supplemental submission contained a rationale for dose selection as based on $LD_{50}$ of 200 mg/kg in Chinese hamsters. Because two doses were given 24 hours apart, two samplings at 24 and 48 hours post-dosing were taken. The criteria for scoring are explained. A total of 12 animals were dosed to ensure that at least 3/sex/group survive and slides prepared with the best ones from 3/sex/group scored. The submission improved the quality of the report. It remained unacceptable based on number of cells scored and no data supporting the sampling times. Therefore, there is no change in status for this particular study. There is an acceptable study for chromosome mutation, however (013, 103 936073, 067217), so EPA and CDFA are in accord with regard to data gap status.

**STUDY TYPE:** Neurotoxicity, hen (study #Siss 5927, Acute Oral Toxicity and Neurotoxicity Study of Technical GS-13005 in the Domestic Fowl, Ciba-Geigy Corporation, No date). CDFA Record No. 935981.

EPA: Forced motor activity and body weight data are not required by the Guidelines.

CDFA: These are required by the Guidelines (81-7, (a) (4)) and have not been provided as of 12/15/89.

1/24/90 for Silva 1/24/90

EPA: It is unlikely that histopathology of the spinal cord (lumbar) and peripheral nerve would alter the conclusions from the study, since there was no clinical evidence of delayed neuropathy following two sequential 21 day dosing periods (with atropine pretreatment).

CDFA: This study has many critical deficiencies and therefore, it would be difficult to speculate on the results. In addition, Ciba-Geigy has not responded to the CDFA review (as of 12/15/89), so the status of the study remains unacceptable.

1/24/90

12/15/89

CASWELL FILE

Revision of EPA 1-liners pertaining to the EPA Memorandum (1/23/89) was performed (12/15/89) by M. Silva.

CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

METHIDATHION (SUPRACIDE)

Chemical Code # 001689, Tolerance # 00298
SB 950 # 094

November 21, 1986
Revised: 11/16/87; 4/29/88; 7/11/88; 10/7/88; 12/17/90; 12/12/91

I. DATA GAP STATUS

| | |
|---|---|
| COMBINATION (CHRONIC & ONCO) RAT: | No data gap; No adverse effect. |
| (CHRONIC & ONCO) MOUSE: | No data gap; Possible adverse effects in both areas. |
| CHRONIC DOG: | Data gap; Inadequate study (upgradeable); Possible adverse effect indicated. |
| REPRODUCTION RAT: | No data gap; No adverse effect. |
| TERATOGENICITY RAT: | No data gap; No adverse effect. |
| TERATOGENICITY RABBIT: | No data gap; No adverse effect. |
| GENE MUTATION: | No data gap; No adverse effect. |
| CHROMOSOME MUTATION: | No data gap; Possible adverse effect. |
| DNA DAMAGE: | No data gap; No adverse effect. |
| NEUROTOX: | No data gap; No adverse effect. |

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**Note, Toxicology one-liners are attached**

All record numbers through 090270 in volume 113 and 89667 in volume 115 were examined.
** indicates an acceptable study.
**Bold face** indicates a possible adverse effect.
File name: T911204
Revised by: B.K. Davis 11/16/87; M. Silva 4/29/88 & 7/11/88; J. Gee 10/7/88; J. Kishiyama & M. Silva, 12/17/90; T. Kellner, 12/12/91.

Gee 12/18/91

T. Kellner 12/17/91

These pages contain summaries only. Each individual worksheet may contain additional effects.

COMBINATION RAT:

** 090 (5 volumes) 053935 "Methidathion - 2-Year Oral Oncogenicity and Toxicity Study in Albino Rats," (CIBA-GEIGY 5/23/86) Methidathion (97.3%) at 0, 4, 40 and 100 ppm in the diet to 80 Sprague-Dawley rats/sex/group in a two year study; 20/sex/group for clinical studies; interim sacrifices of 10/sex/group at 52 weeks and 5/sex/group at 93 weeks; oncogenicity NOEL > 100 ppm; chronic toxicity NOEL = 4 ppm (skin lesions/sores with ulceration and inflammation, transient neurological effects, altered blood parameters, altered biochemical parameters, reduced liver weights, alveolar foamy macrophages) No adverse effect; ACCEPTABLE. (Davis 10/28/87).

COMBINATION MOUSE:

** **079 through 087 45719-45727** "Two Year Dietary Oncogenicity Study in Mice," International Research and Development Corp., 3/7/86; Methidathion Technical (purity not stated) at 0, 3, 10, 50, and 100 ppm by feeding to 50/sex/dose for 23 months in the oncogenicity phase and to 120/sex/dose with 4 interim sacrifices before the termination at 18 months of the chronic toxicity phase. This includes a group given a one month recovery period on control feed and then sacrificed at 13 months. **Possible chronic toxicity adverse effect:** increased mortality, discolored urine in males at high doses, some elevated blood enzymes, altered cholinesterase levels, multiple liver and gallbladder changes, some spleen changes. NOEL = 10 ppm = 1.2 to 2.0 mg/kg/day. **Possible oncogenicity adverse effect:** increased frequencies of hepatocellular adenomas and carcinomas as well as nonneoplastic hepatic and bilary changes in males at 50 and 100 ppm, increased frequencies of nonneoplastic hepatic changes in females at 100 ppm. Complete ACCEPTABLE. (B. Davis, 11/14/86)

CHRONIC RAT:

A possible adverse effect was identified in the following study based on the slight increase in the frequency of degenerative liver changes in high dose animals. Noting that this effect was slight and that the study had numerous deficiencies which made it unacceptable, the present reviewers are more convinced by the lack of chronic toxicity in the acceptable combined rat study (Record 053935). The high dose (100 ppm) in the combined study was somewhat greater than that of the chronic study (64 ppm), yet no degenerative liver changes were found. B. Davis, 1987.

**010 935997** "Safety Evaluation by 2-Year Feeding Studies in Rats and Dogs - GS 13005, 40W - Rat Study," Woodard Research, 1/6/67; Rat chronic toxicity (831). Methidathion (GS 13005 - 40% wettable powder, purity not stated) at 0, 4, 16, 64 ppm in feed to 25/sex/dose for 100 weeks; **Possible adverse effect**--degenerative liver changes, decreased adrenal-to-body and ovary-to-body weights, increased kidney ratios, decreased body weight gain. NOEL <4 ppm. Incomplete UNACCEPTABLE. High mortality (85/200) from pulmonary infections, hematology sampling insufficient, blood biochemistry too limited, missing individual data, incomplete histopathology. (J. Remsen, 7/5/85, Davis 11/10/87)

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T. Kellner 1/7/9

298-076 Technical information on Supracide: the information listed below was obtained from data summaries prepared by Ciba-Geigy Corp. 1968-69.
No worksheets were prepared (the descriptions of methods and results are incomplete and none of the studies meet EPA-FIFRA guidelines). Some of the studies from the data volume are described under other sections in this tox. summary (T. Kellner, 12/12/91):

-076 47483 Dermal toxicity of methidathion in rats. Three groups of rats (3 males and 3 females per group) were given technical A.I. (1.5 mg/kg/day) or 40% wettable powder formulation or 40% emulsifiable concentrate (40% product dosage was 54 mg/kg/day) by application to shaved skin. The rats were immobilized for 3 hours to allow absorption, after which the application areas were wiped with a damp sponge. All dosed animals showed cholinergic symptoms but no mortality or local irritation.

-076 47486 Subchronic toxicity in rats. Rats (male and female, 5 each) were dosed by oral gavage, 6 days per week at 2.5, 5.0, 10.0 and 20.0 mg/kg/day for 4 weeks. Mortality of 4/10 and 9/10 at 10 and 20 mg/kg doses, respectively; reduction in weight gain in all dose groups. Cholinergic symptoms were noted in the 5, 10 and 20 mg/kg groups. No gross changes were seen in organs of rats alive at 28th day. Histopathologic changes in liver: fatty deposits described as systematized centro-medio-lobular deposits without degeneration.

-076 47487 Subchronic toxicity in rats (2 and 4 week exposures). Rats (10/dose) received 16.6 and 33.2 mg/kg/day for 2 weeks or 0.25, 0.83, 2.5, 8.3 mg/kg/day for 4 weeks by oral gavage. All of the high dose and half of the 16.6 mg/kg group died during the first 4 days of dosing. Erythrocyte ChE activity was 16% of control after 4 weeks in the 8.3 mg/kg group while plasma ChE (PChE) was 73% of control. PChE levels were observed after compound administration had stopped (time period was not specified). PChE was reported to return to normal within 3 days, but EChE required 21 days to reach 75% of normal.

-076 47488 Subchronic feeding study in rats. Rats (24 males and females/dose) were fed 0, 1, 4, 16 and 64 ppm methidathion for 4 to 22 weeks. Interim sacrifices were performed to obtain brain ChE levels in addition to ChE activity in RBCs and plasma. Brain and RBC ChE inhibition were comparable: 16 ppm resulted in 25 to 30% inhibition and 64 ppm resulted in 70-80% ChE inhibition. Plasma ChE showed little or no dose effect.

-076 47489 Subchronic feeding study in rats. Rats (20 males and 20 females) were administered 0, 0.5, 2, 10, 50 and 250 ppm methidathion for 6 months. High-dose rats showed fine fibrillation in the extremities; females showed hyperexcitablility with fine whole body muscular tremor during the 7th week. RBC ChE more sensitive than that of plasma or brain. ChE NOEL = 2 ppm (0.2-0.24 mg/kg/day).

298-018 Contains methidathion residue data on alfalfa and cotton and duplicates of toxicology studies found in volume 298-076.

CHRONIC DOG:

**010 33538** "Safety Evaluation by 2-Year Feeding Studies in Rats and Dogs - GS 13005, 40W - Dog Study," Woodard Research, 1/6/67; Methidathion (GS 13005 - 40% wettable powder, purity not stated) at 0, 4, 16, 64 ppm in feed 6 days/week for 105 weeks to 3 Beagles/sex/dose. **Possible adverse effect**--dark liver pigmentation, some pigmentation of hepatic cells, slight kidney cell pigmentation, altered plasma enzyme levels suggestive of altered liver

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metabolism. NOEL = 4 ppm. Incomplete, UNACCEPTABLE. Too few animals, missing electrolyte balance data, insufficient histopathology, no food consumption data. (J. Remsen, 7/5/85).
EPA 1-liner: Core Minimum.

**298-115 89667** Chang, J. and Walberg, J. "1-Year Dietary Toxicity Study with GS-13005 in Beagle Dogs" (Ciba-Geigy Corp., Lab Study No.: F-00028, 6/24/91). Methidathion technical (GS-13005), lot FL-890331, purity of 96%, was administered in the feed at nominal concentrations of 0 (control), 0.5, 2, 4, 40 or 140 ppm (corresponding to mean daily dosages in males: 0.02, 0.07, 0.15, 1.33 and 4.51 mg/kg/day; in females: 0.02, 0.07, 0.15, 1.39 and 4.90 mg/kg/day) to 4 beagle dogs/sex/dose level for 1 year. Food consumption was reduced in 140 ppm males; brain and RBC cholinesterase (ChE) was significantly inhibited in 140 ppm males and females. Cholinergic NOEL = 4 ppm (inhibition of RBC ChE also noted at 40 ppm). **Possible Adverse Effect:** Liver lesions (elevated serum bilirubin and enzyme activities, decreased serum albumin and total protein and moderate to severe cholestasis and liver discoloration (gross necropsy) at 40 and 140 ppm). NOEL = 4 ppm (0.15 mg/kg/day). **Unacceptable.** Description of analytical methods was inadequate. **Upgradeable.** (Kellner and Gee, 11/18/91).

CHRONIC MONKEY:

014 935999 "Two-Year Safety Evaluation in Rhesus Monkeys," Institute of Experimental Pathology & Toxicology, 4/71; Methidathion (GS 13005, purity not stated) at 0 mg/kg (7 males and 5 females), 0.25 mg/kg (6/sex), 1.0 mg/kg (7 males and 5 females) by gavage 6 days/week for 23 months to Rhesus monkeys. RBC and plasma cholinesterase somewhat depressed. Chronic toxicity NOEL = 1.0 mg/kg. Insufficient information to assess possible adverse effect. Incomplete UNACCEPTABLE. Only two dose levels and high dose too low; missing histopathology, individual data. (J. Remsen, 7/8/85)

ONCO MOUSE:

This mouse oncogenicity study (935007) and the mouse combination study (see Records 45719-45727 above) are consistent in indicating induction of liver adenomas and carcinomas. The data gap is filled by the combination study. Davis, 1987.

**016 936007** "Carcinogenicity Evaluation with Methidathion Technical in Albino Mice," Industrial Biotest Laboratories #8580-09380, 5/2/80; EPA Tracking System Report (7/83) rates the study as Supplemental (portions of the study are valid), Pending (still under review), and Replaced (done or in progress); Validation review by registrant in accordance with EPA criteria included (Reports 2 & 4, Record #936006, Vol. 016); Methidathion (98.8% purity) at 0, 10, 100 ppm in feed to 60/sex/dose over 18 months for males and 19 months for females. **Possible adverse effect**--liver adenomas and carcinomas, spleen nodules. NOEL = 10 ppm. Incomplete, UNACCEPTABLE. High dose insufficient to produce chronic toxicity; no food consumption data; negative control group mistakenly dosed in month 14; apparent degradation of test material in first 8 months; no hematology. (J. Remsen, 7/8/85)

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REPRO RAT:

097 55142 "Two-Generation Reproduction Study in Albino Rats with Methidathion Technical." Pilot study for 55143. M. Silva, 2/3/88.

** 298-098 55143 "Two-Generation Reproduction Study in Albino Rats with Methidathion Technical," (American Biogenetics Corporation Study 450-2125, 1/15/87). Methidathion technical, 95%, was given to CR1:CD BR rats in the diet at 0, 5, 25 or 50 ppm for a two generation, 1 litter per generation reproduction study (15 males and 30 females/dose group). Parental NOEL = 5 ppm (decreased: body weight gain--F0 females & F1 both sexes at 50 ppm, food consumption--F0 females at 25 & 50 ppm & F1 both sexes at 50 ppm, liver & ovary or testes weights--F0 & F1 both sexes at 50 ppm, mating index--F0 & F1 males at 50 ppm; also poor maternal care and tremors during lactation were observed--F0 & F1 dams at 25 & 50 ppm). Reproductive NOEL = 5 ppm. Lower survival and body weights were observed in progeny of both generations at 25 and 50 ppm. No adverse effect. ACCEPTABLE. D. Shimer, 12/8/87. M. Silva, 1/28/88.

**018, 076 33539** "GS 13005, 40W - Three-Generation Reproduction Study in the Rat," Woodward Research, 8/18/66; Methidathion (40% wettable powder) at 0, 4, 32 ppm in feed to 10 males and 20 females over 3 generations. **Possible adverse effect**--decreased weanling survival in most litters. NOEL = 4 ppm. Incomplete, UNACCEPTABLE. Report is summary with one data table. (J. Remsen, 7/8/85).

**298-076 47484** GS 13005 - "Effect on Reproduction", Fisons Pest Control Limited, FPCL Report Tox/117/6, 11/65. Eight female and four male rats were fed 50 ppm technical methidathion for 3 months; same number of rats served as controls. RBC ChE activity in treated rats was reduced to about 20-40% of control levels. Mean litter size was reduced in the treated animals, but the difference was not significant by Student's "t" test ($p>0.1$). Not a guideline study; summary report only. (T. Kellner, 12/11/91).

Summary: The more recent, acceptable study did not indicate reproductive effects in the absence of parental toxicity. Therefore, the possible adverse effect in the summary report was not confirmed. Overall, there is not an adverse effect on reproduction. Gee, 10/7/88.

TERATOLOGY RAT:

094 55138 "Methidathion Technical: A Dose Range finding study in Pregnant Rats (MIN852171)." Pilot study for 55139. M. Silva, 2/3/88.

** 298-095 55139 "Methidathion Technical - A Teratology (Segment II) Study in Rats (MIN 862164)," (Ciba-Geigy, Research Department, Pharmaceuticals Division, Report no. 86172, 1/15/87). Methidathion technical, 95%, was given to mated Crl:COBS CD (SD) BR rats (25/group) by gavage on days 6-15 of gestation (day 0 = presence of sperm in vaginal washing), at 0 (3% cornstarch with 0.5% Tween 80), 0.25, 1.0 or 2.5 mg/kg/day. Fetuses were delivered by Caesarean section on gestational day 20. **No adverse effects.** Maternal NOEL = 1.0 mg/kg/day, (mortality, reduction in food consumption and body weight gain, lethargy, tremors, lacrimation, salivation, raspy respiration, exophthalmia and vaginal blood). Developmental NOEL $\geq$ 2.5 mg/kg/day. ACCEPTABLE. (D. Shimer, 12/7/87. M. Silva, 1/25/88).

12/18/91

T. Kellner 12/19/91

072 1179 "Reproduction Study on GS13005 Technical: Rat," Ciba-Geigy Limited, Basel, Switzerland 2/9/76; Methidathion (GS 13005 Technical, no purity stated) by gavage to female rats on days 6-15, 0 mg/kg to 24 rats, 1 mg/kg to 28 rats, 2.5 mg/kg to 23 rats, 5.0 mg/kg to 21 rats. Maternal toxicity--decreased food intake and body weight gain, tremors. NOEL = 1 mg/kg. Developmental toxicity--incompletely ossified fifth sternebrae. NOEL = 2.5 mg/kg. Insufficient information to assess possible adverse effects. Incomplete, UNACCEPTABLE. No individual data, body weight data, uterine weight data, dam autopsy, fetal sex data, corpora lutea data. (J. Remsen, 7/8/85)

TERATOLOGY RABBIT:

096 55141 "Rabbit - Segment II- Dose Range- Find Teratology Pilot (P-2) Methidathion (MIN 852223)." Pilot Study for 55140. M. Silva, 2/3/88.

** 096 55140 "Methidathion A Teratology (Segment II) Study in Rabbits (MIN 852202)," (Ciba-Geigy, Research Department, Pharmaceuticals Division, Report No. 86131, 1/13/87). Methidathion technical, 95%, was administered to inseminated New Zealand White Rabbits by gavage on days 7-19 of gestation (day 0 = day of artificial insemination) at 0, (3% cornstarch containing 0.5% Tween 80), 2, 6 or 12 mg/kg/day (19/group). Fetuses were delivered by Caesarean section on gestation day 29. No adverse effect. Maternal NOEL = 6 mg/kg/day, (ataxia, tremors and salivation). Developmental NOEL $\geq$ 12 mg/kg/day. ACCEPTABLE. (D. Shimer, 12/8/87. M. Silva, 1/25/88).

GENE MUTATION:

Following are one-liners for gene mutation assays. The 7 Ames Salmonella assays (4 with methidathion and 3 with related compounds) and one E. coli assay include results from 3 different laboratories. The remaining 3 studies are host-mediated assays. Although none of the 11 studies was in itself acceptable, together they present a consistent and compelling picture of no mutagenicity. Therefore the data gap is filled and there is no evidence for an adverse effect. (Davis, 1987).

003 936024 "Salmonella/Mammalian-Microsome Mutagenicity Test with GS 13005," Ciba-Geigy Limited, Basel, Switzerland 4/17/80. Methidathion (GS 13005 - purity not stated) at 0, 25, 75, 225, 675, 2025 ug per 0.1 ml $\pm$ activation with triplicate plates of strains TA98, TA100, TA1535, TA1537. Insufficient information to assess mutagenicity. Incomplete, UNACCEPTABLE. Positive control with activation done only with TA1535, missing individual plate data, deficient test article characterization. (J. Remsen, 7/3/85)

003 936025 "Salmonella/Mammalian-Microsome Mutagenicity Test with GS 13005," Ciba-Geigy Limited, Basel, Switzerland, 10/29/80. Methidathion (GS 13005 - purity not stated) at 0, 25, 75, 225, 675, 2025 ug per 0.1 ml $\pm$ activation with triplicate plates of strains TA98, TA100, TA1535, TA1537. Insufficient information to assess mutagenicity. Incomplete UNACCEPTABLE. Positive control with activation done only with TA1535, missing individual plate data, deficient test article characterization. (J. Remsen, 7/3/85)

003 33537 "In Vitro Microbial Assays for Mutagenicity Testing of DMTP (Methidathion) - Reverse Mutation - Plate Method Using S. typhimurium," Nomura Research Institute, Japan 8/31/79. Methidathion (99.95% purity) at 0, 10, 50, 100, 500, 1000, 5000 ug/plate $\pm$ activation using TA98, TA100, TA1535,

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TA1537, TA1538. Insufficient information to assess mutagenicity. Incomplete, UNACCEPTABLE. No confirmatory assay, positive control results for TA1535 with activation and TA98 without activation both questionable, duplicate rather than triplicate plates/concentration, missing individual plate data. (J. Remsen, 7/3/85)

003 936020 "In Vitro and In Vivo Microbiological Assays of Six Ciba-Geigy Chemicals-Ames Microbial Mutagenesis Assay", Stanford Research Institute, 3/77. Methidathion (purity not stated) at 0, 10, 50, 100, 500, 1000, 5000 ug/plate ± activation using TA98, TA100, TA1535, TA1537, TA1538 with confirmatory assay. No mutagenicity indicated. Incomplete UNACCEPTABLE. No statement of number of plates/concentration, no statistics, missing individual plate data, too little test article characterization, some positive controls not done or ineffective. (J. Remsen, 7/5/85)

003 936020 "In Vitro and In Vivo Microbiological Assays of Six Ciba-Geigy Chemicals-Host Mediated Assay", Stanford Research Institute, 3/77. Methidathion (purity not stated) in acute assay with a single dose of 0, 10, 20, 40 mg/kg and subacute assay with 0, 5, 10, 20 mg/kg for 5 days. The number of mice ranged from 6-10 per group. Salmonella strains TA1535 and TA1538 injected ip and recovered from peritoneal cavity after 4 hours. Insufficient information to assess mutagenicity. Incomplete UNACCEPTABLE. No evidence for actual exposure of bacteria to test material, missing individual plate data, deficient test article characterization. (J. Remsen, 7/5/85)

003 33536 "In Vitro Microbial Assays for Mutagenicity Testing of DMTP (Methidathion) - Reverse Mutation - Plate Method Using E. coli," Nomura Research Institute, Japan 8/31/79; Methidathion (99.95% purity) at 0, 10, 50, 100, 500, 1000, 5000 ug/plate ± activation using strain WP2 Hcr-. Negative for mutagenicity. Incomplete UNACCEPTABLE. No confirmatory assay, duplicate rather than triplicate plates/concentration, missing individual plate data. (J. Remsen, 7/3/85)

003 936026 "Intrasanguine Host-Mediated Assay with S. typhimurium with GS 3005," Ciba-Geigy 10/31/80. Methidathion (purity not stated) administered orally to groups of 6 mice at 0, 5, 10, 20 mg/kg/hour for 3 doses with Salmonella strains TA98, TA100, or TA1537 injected into the tail vein immediately after the third dose. Bacteria recovered from homogenized liver after one hour and assayed for the number of mutants. Insufficient information to assess mutagenicity. Incomplete UNACCEPTABLE. No evidence for actual exposure of bacteria to test material, no positive control, lacks TA1535, excessive mortality, missing individual plate data, deficient test article characterization. (J. Remsen, 7/3/85)

003 936022 "Salmonella/Mammalian-Microsome Mutagenicity Test with GS 12956" Ciba-Geigy, Basel, Switzerland 10/27/80. Methidathion metabolite (GS 12956 - purity not stated) at 0, 10, 30, 90, 270, 810 µg per 0.1 ml ± activation with triplicate plates of TA98, TA100, TA1535, TA1537. Insufficient information to assess mutagenicity. Supplementary Study-assay of metabolite. (J. Remsen 7/5/85).

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003 936018 "Salmonella/Mammalian-Microsome Mutagenicity Test with GS 28370," Ciba-Geigy ltd., Basel, Switzerland, 10/24/80; Sulfone derivative of methidathion (purity not stated) at 0, 25, 75, 225, 675, 2025 ug per 0.1 ml ± activation with triplicate plates of TA98, TA100, TA1535, TA1537. Insufficient information to assess mutagenicity. Supplementary study-assay of sulfone derivative. (J. Remsen, 7/5/85).

003 936023 "Salmonella/Mammalian-Microsome Mutagenicity Test with GS 28369," Ciba-Geigy, Basel, Switzerland, 12/15/80. Sulfone derivative of methidathion (purity not stated) at 0, 15, 30, 60, 120, 240, 480, 960 ug per 0.1 ml ± activation with duplicate plates of TA98, TA100. Insufficient information to assess mutagenicity. Supplementary study-assay of sulfone derivative. (J. Remsen, 7/5/85)

Mammalian cells

003 936017 "Point Mutation Assay with Mouse Lymphoma Cells, Host Mediated Assay with GS 13005," Ciba-Geigy, Basel, Switzerland, 10/21/80. Methidathion (purity not stated) given orally at 0 or 15 mg/kg to 4 mice/dose, 3 days after ip inoculation of mouse L5178Y cells. 3 days after methidathion dosing, L5178Y cells removed from peritoneal cavity and tested for forward mutation. Insufficient information to assess mutagenicity. Incomplete UNACCEPTABLE. No evidence for actual exposure of cells to test material, no positive control, deficient detail on cell viability or replicates, no GLP, deficient test article characterization. (J. Remsen, 7/5/85)

CHROMOSOME MUTATION:

An overall conclusion cannot be made from the four chromosome mutation studies which have been submitted. The SCE study had a significantly elevated frequency at the intermediate dose but not at the high dose. The two micronucleus assays and the dominant lethal assay were all negative. Furthermore, one of the micronucleus assays was a supplementary study with a methidathion metabolite. The data gap is filled but in the absence of better evidence a possible adverse effect is identified. Davis, 1987 and Gee, 10/7/88.

**003, 103 936027, 067219** "Sister Chromatid Exchange Study - GS 13005 - Chinese Hamster." (Ciba-Geigy, Basle, Switzerland, 11/4/80, supplement dated 5/26/87) Methidathion, Batch op. 25-572, 93.4%; tested at 0 (0.5% aqueous carboxymethylcellulose), 17, 34 or 68 mg/kg by oral gavage given once; BrdU given 2 hours before the test material; 4/sex/group Chinese hamsters; sacrificed after 24 hours; examined slides from 2/sex/group only, 25 cells per animal scored; **possible adverse effect** with statistically increased SCEs ($p < 0.01$) at mid dose. Record # 067219 contains purity, batch number, explanation of using only 2/sex. UNACCEPTABLE (inadequate number of animals/cells scored especially in view of the elevation in sister chromatid exchanges at the mid dose. No change in status with submission of supplemental information. Gee, 7/5/85 and 10/6/88.
EPA 1-liner: Core acceptable.

003, 103 936021, 067218 "Nucleus Anomaly Test in Somatic Interphase Nuclei of Chinese Hamster." (Ciba-Geigy, Basle, Switzerland, 7/2/80, supplement dated 5/26/87) Methidathion, 96.9%, given by oral gavage at 0 (CMC), 17, 34 or 68 mg/kg twice at a 24 hour interval; sacrifice at 24 hours after the second dosing; 6/sex/group with the best slides from 3 animals per

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sex per group scored; 1000 bone marrow cells per animal; micronucleus test; initially reviewed by J. Remsen, 7/5/85, as unacceptable based on number of animals examined, the single sacrifice time and dose selection not justified. Record # 067218 in 103 describes the criteria used, the selection of doses and slides for scoring. No change in status. No increase in micronuclei formation. UNACCEPTABLE (inadequate number of animals scored, no data supporting the sacrifice time.) Gee, 10/5/88.

** 013, 103 936073, 067217 "Dominant Lethal Study in GS 13005 - Mouse." (Ciba-Geigy, Basel, Switzerland, 8/3/76 and 5/26/87) Methidathion, Batch No. 32289/4239, 98.4%; given by gavage to 20 male NMRI mice per group at 0 (carboxymethylcellulose), 15 or 45 mg/kg; mated over 6 weekly periods at 1 male to 2 females; toxicity included ataxia, diarrhea, somnolence, convulsions and 4/20 deaths at the high dose; no dominant lethal effects reported; initially reviewed as unacceptable (lack of purity, no positive control data) - Remsen, 7/8/85. Record # 067217 contains purity and positive control data with thiotepa in the same strain of mice in the same year. Upgraded to ACCEPTABLE status. Gee, 10/5/88.

003 936028 "Nucleus Anomaly Test in Somatic Interphase Nuclei - GS 12956 - Chinese Hamster Test for Mutagenic Effects on Bone Marrow Cells" Ciba-Geigy, Basel, Switzerland, 10/30/80. Methidathion metabolite (GS 12956 - purity not stated) at 0, 121, 242, 484 mg/kg/day for 2 days by gavage to 3/sex/dose. Sacrificed 24 hours after second dose and 1000 bone marrow cells/animal evaluated. Micronucleus assay protocol, though scored other nuclear anomalies as well. Insufficient information to assess possible adverse effect. Supplementary Study-assay of metabolite. (J. Remsen 7/5/85)

DNA DAMAGE:

In addition to the two acceptable (113, 087194 and 089, 113, 053776, 087195) and four unacceptable studies in this category, there is also an SCE study (see Record 936027 in the Chromosome Mutation category), which can be used in this category. As noted above, the frequency of SCEs was significantly elevated only at the middle dose level. This was identified as a possible adverse effect for the Chromosome Mutation category but will not be considered further here. The studies summarized below were all negative, therefore there is no adverse effect indicated for methidathion in the DNA damage category. M. Silva, 1990.

** 113 087194, "Autoradiographic DNA Repair Test on Rat Hepatocytes", (T. Hertner, CIBA-GEIGY Limited, Basle, Switzerland, Laboratory Study Number 891344, 2/6/90). GS 13 005 technical (purity 96.0%, Batch #: op. 709514) was assayed at concentrations of 0 (vehicle = DMSO), 1.85, 5.56, 16.67, 50, 100, and 200 µg/ml using primary hepatocytes from adult male (Tif.RAIf(SPF)) rats (4 cultures/dose were treated and 3/dose were used for data assessment, 50 nuclei/slide were assessed) in a 16-18 hour exposure. The original test was followed with a repeat assay. Net grains per nucleus did not increase sufficiently to suggest genotoxicity, in either test. ACCEPTABLE. (Kishiyama & Silva, 12/10/90)

** 089, 113 053776, 087195, "Autoradiographic DNA Repair Test on Rat Hepatocytes", (T. Hertner, CIBA-GEIGY Limited, Basle, Switzerland, Laboratory Study Number 820585, 10/19/82 & 12/9/88). GS 13 005 (purity 97.2%, Batch #: op. 204485) was assayed at concentrations of 0 (untreated cells or DMSO), 0.128, 0.64, 3.2, and 16 µg/ml (triplicate slides & 50 cells/slide) using primary hepatocytes from adult male (Tif.RAIf(SPF)) rats. Exposure time was

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for 5 hours. The original review (Hughett & Davis, 10/28/87--089 053776) concluded no adverse effects were indicated but the study was incomplete (too little information on test material, protocol, and results; background radioactivity on the slides was not counted; page 5 was missing). After submission of the requested information (113 087195) the study has been upgraded to **acceptable** status. (Kishiyama & Silva, 12/10/90)

003 936019 "In Vitro Microbial Assays for Mutagenicity Testing of DMTP (Methidathion) - Rec Assay" Nomura Research Institute, Japan, 8/31/79. Methidathion (99.95% purity) at 0, 250, 500, 1250, 2500, 5000, 10000 ug/well without activation using paired Bacillus subtilis strains H17 and M45. Negative for mutagenicity. Incomplete, UNACCEPTABLE. No activation included, reference to publication rather than detailed protocol. (J. Remsen, 7/3/85)

089 53774 "The Hepatocyte Primary Culture/DNA Repair Assay on Compound GS-13005-008266 Using Mouse Hepatocytes in Culture." (Naylor Dana Institute 2/10/82) Methidathion = GS-13005-008266 (No purity stated) tested at 14 concentrations from $5 \times 10^{-7}$ to 1%; cytotoxicity at levels > $5 \times 10^{-3}$%; No increase in UDS indicated, Incomplete, UNACCEPTABLE (need substance purity and grade, number of cells examined). Davis 10/28/87.

089 53775 "The Hepatocyte Primary Culture/DNA Repair Assay on Compound GS-13005-008266 Using Rat Hepatocytes in Culture." (Naylor Dana Institute 2/10/82) Methidathion = GS-13005-008266 (No purity stated) tested at 10 concentrations from $5 \times 10^{-9}$ to 1%; cytotoxicity at levels > $5 \times 10^{-2}$%; No increase in UDS indicated, Incomplete, UNACCEPTABLE (need substance purity and grade, number of cells examined). Davis 10/28/87.

089 53777 "Autoradiographic DNA Repair Test on Human Fibroblasts - GS 13 005 (In vitro test for DNA-damaging properties)." (Ciba-Geigy Ltd. 10/18/82) Methidathion = GS 13 005 (no purity stated) tested at 1.024, 5.12, 25.6, and 128 ug/ml; 5 uM 4-nitroquinoline-N-oxide as positive control; No adverse effect reported, Incomplete, UNACCEPTABLE, Not Upgradeable (No activation system used, background grain counts not done, missing protocol information, missing test material information, missing results) Davis 10/28/87.

NEUROTOX:

** 110 090269 & 090270 "Acute Delayed Neurotoxicity of Methidathion Tech FL 890331 in Domestic Fowl," (Kuhn, J.O., Stillmeadow, Inc., Lab No. 6300-89, 12-18-89). Methidathion technical (FL890331, batch OP709514, 96.5% pure) dissolved in corn oil was administered to domestic hens (60/test group--protected by atropine, administered at 5, 20.5, 25.5 and 29 hours after dosing) by gavage at 145 mg/kg on day 1, then 21 days later. The negative control group was given corn oil only (10/group). The positive control group was given TOTP at 500 mg/ml (8 hens) one time. 22 hens died by day 4, after the first dose and a total of 8 showed some degree of unsteadiness during the observation period. An additional 6 animals died within 2 days of the second dosing but no definitive signs of neurotoxicity were observed. Histopathology revealed no lesions indicative of neuropathy while TOTP treated hens had typical lesions. **No adverse effect. Acceptable.** M. Silva, 12/12/90.

012 935981 "Neurotoxicity Study in Domestic Fowls, 42 Days - Using GS 13005," Ciba-Geigy, no date. Technical methidathion (GS 13005 -no purity stated) by gavage after pretreatment with atropine sulfate, observed for 21 days, repeated dose and 21 day observation; 0 mg/kg to 10 hens, 43.75 mg/kg to 15 hens, 87.5 mg/kg to 15 hens, 175 mg/kg to 30 hens, 350 mg/kg to 30 hens.

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Insufficient information to assess possible adverse effect. Incomplete UNACCEPTABLE. No forced motor activity, no body weight data; no histopathology on thoracic spinal cord or medulla oblongata. (J. Remsen, 7/5/85)

EPA 1-liner: Core Guideline.

298-076 935971 "Neurotoxic effects in the Hen", Fisions Pest Control Limited, FPCL Report Tox/117/5. Four adult hens treated by subcutaneous injections of 50 mg/kg methidathion technical in glycerol. No symptoms of delayed neuropathy were observed in the 8 week observation period that followed. Not a guideline study; summary report only. (T. Kellner, 12/11/91).

076 16554 "Toxicology of GS 13005 - Neurotoxicity," Conducting Laboratory not identified, no date. Methidathion (GS 13005 - no purity stated) given by 4 weekly subcutaneous injections to 4 hens at 50 mg/kg. Report is a very a brief summary with insufficient information for assessment. Incomplete UNACCEPTABLE. No protocol, data summaries, individual data, negative or positive control groups. (J. Remsen, 7/8/85)

076 14846 "GS-13005, 40 W - Demyelination Study in the Chicken," Woodard Research, 6/18/65. Methidathion (GS 13005 - 40% wettable powder) fed for 45 days to 10 hens/dose at 16, 52, and 160 ppm. Report is a summary with insufficient information for assessment. Liver discoloration at high dose. Incomplete UNACCEPTABLE. No protocol, data summaries, individual data, negative control group. Since feeding study, not appropriate for acute delayed neurotoxicity. (J. Remsen, 7/8/85)

ADDITIONAL STUDIES

DERMAL ACUTE, RABBIT:

091 55134 "Rabbit Acute Dermal Toxicity." (Stillmeadow Inc., Houston, Texas, project no. 4272-86, 8-27-86) Methidathion 50S, 50.9%, was dermally applied (non-occlusion) to 5 male and 5 female New Zealand White Rabbits for a period of 24 hours at 2010 mg/kg. The rabbits were observed for 14 days. No adverse effects. $LD_{50}$ > 2010 mg/kg. (1 death occurred, diarrhea, lacrimation, nasal discharge, activity decrease, absent or decreased urination and defecation; gastrointestinal tract distended with gas). Supplemental Study (analysis of formulated material is required). (Shimer, 12-14-87. M. Silva, 2/3/88).

DERMAL SUBCHRONIC RABBIT:

-076 935992 21-Day Subacute Dermal Toxicity Study (Rabbits). Industrial Bio-Test Laboratories, August 5, 1969. Methods and dose levels were not described. Results: An increase in the total leukocyte count, increase in the percent of neutrophils and a decrease in percent of lymphocytes was noted at a level of 76.8 mg/kg. A 15% decrease in plasma ChE activity and 26% decrease in erythrocyte activity was noted at 38.4 mg/kg level; inhibition of 17% plasma ChE activity and 39% inhibition of erythrocyte activity occurred at 76.8 mg/kg. Not a guideline study. (T. Kellner, 12/12/91).

092 55136 "10-Day Dermal Dose Range Finding Study in Rabbits with Methidathion Technical." (Hazleton, Vienna, VA, Study No. 483-253, 1-16-87). Pilot Study for 55135 and 55137. (M. Silva, 2/3/88).

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092 55135 "Methidathion 21-Day Dermal Toxicity Study in Rabbits (MIN 852128)." (Ciba-Geigy, Research Department, Pharmaceuticals Division, report no. 86019, 8-28-86) Methidathion technical, 95%, was administered to New Zealand White rabbits dermally (non-occlusion exposure) for 6 hrs/day for 22 consecutive days at 0 (polyethylene glycol 300), 1, 5 or 20 mg/kg/day, 5/sex/group. NOEL > 20 mg/kg/day. One high dose male exhibited hypoactivity, diarrhea, soft feces and decreased food consumption. High dose males as a group had a minimal (not significant) decrease in body weight. No adverse effects. Supplemental Study. No MTD reached. (Shimer, 12-15-87. M. Silva, 2/3/88).

**093 55137** "21-Day Dermal Toxicity Study in Rabbits with Methidathion Technical." (Hazleton, Vienna, VA, study no. 483-254, 1-16-87) Methidathion technical, 95%, was administered to New Zealand White rabbits dermally (rubber dam occlusion), 6 hours/day for 21 consecutive days at 0 (polyethylene glycol 400), 1, 10, 40 or 80 mg/kg, 5/sex/group. Deaths include 2 at 1 mg/kg, 2 at 10 mg/kg, 5 at 40 mg/kg and 7 at 80 mg/kg. Clinical symptoms increased with increasing dose. They included anorexia, languid behavior, ataxia, hunched posture, labored respiration, soft feces, low body temperature and tremors. Plasma, RBC and brain cholinesterase was significantly reduced at ≥ 10 mg/kg. **Adverse effects indicated.** In the liver, capsular/subcapsular necrosis and acute inflammation was observed in females at 10, 40 and 80 mg/kg. The gallbladder of females in the 10, 40 and 80 mg/kg and males in the 80 mg/kg groups showed caseous necrosis with hemorrhage and chronic serosal inflammation. Supplemental study. (Shimer, 12-15-87. M. Silva, 2/2/88).

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| **Chemical:** | **Methidathion** |
| **PC Code:** | **100301** |
| **HED File Code** | **13000 Tox Reviews** |
| **Memo Date:** | **01/23/89 12:00:00 AM** |
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